REMARKS/ARGUMENTS

Discussion of Claim Amendment

Claim 47 has been amended to recite that the method is directed to treating human immunodeficiency virus (HIV) infection in an antiretroviral treatment-experienced mammal. In addition, the language relating to the description of the mutant virus towards the end of the claim has been deleted as unnecessary. Claims 61-63 have been amended to further polish the claim language. Claims 81-82 have been added and is directed to embodiments of the invention. No new matter has been added.

The Office Action

Claims 47 and 49-80 are currently pending and stand rejected under 35 USC 103(a), as allegedly unpatentable over Vazquez et al. (WO 95/06030). The Office states that Vazquez et al. teaches that the compounds disclosed therein are effective as retroviral protease inhibitors, particularly as inhibitors of HIV protease. The Office admits that Vazquez et al. fails to teach the administration of the compounds to an HIV infected mammal. However, the Office contends that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer the composition to an HIV infected mammal. The Office contends that there is motivation to do so, the alleged reason for such a motivation being the desire to inhibit the action of HIV proteases. The Office also contends that one of ordinary skill in the art would have had a reasonable expectation of success for doing so for the stated reason that Vazquez et al. teaches that the compound inhibits HIV proteases.

Discussion

Applicants respectfully disagree with the Office Action. A determination of obviousness under 35 USC § 103(a) is a legal conclusion based on factual evidence. See *Burlington Indus., Inc. v. Quigg,* 822 F.2d 1581, 3 USPQ 2d 1436 (Fed. Cir. 1987). The factual evidence derives from the analysis mandated by *Graham v. John Deere Co.,* 383 U.S. 1, 148 USPQ 459 (1966), which requires an inquiry into: (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed subject matter, (3) the level

of ordinary skill in the art at the time the invention was created. (see, e.g., *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.2d 14, 57 USPQ 2d 105(Fed. Cir. 2000); and (4) any objective evidence of nonobviousness. See, e.g., *Weatherchem Corp. v. J.L. Clark, Inc.*, 163 F. 3d 1326, 49 USPQ 2d 1001 (Fed. Cir. 1998). As objective evidence of nonobviousness, an Examiner should consider evidence of long-felt need and failure by others. See, e.g., *In re GPAC Inc.*, 57 F. 3d 1573, 35 USPQ 2d 1116 (Fed. Cir. 1998).

To establish a *prima facie* case for obviousness, the Office must satisfy *three* requirements: (1) the prior art reference or combination of references must teach or suggest *all the limitations* of the claims to those of ordinary skill in the art. See *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art."); (2) the prior art relied upon must contain some suggestion or incentive, coupled with knowledge generally available in the art at the time of the invention, that would have motivated those of ordinary skill in the art to modify a reference or combine the references. See, *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1385, 58 USPQ2d 1286, 1293 (Fed. Cir. 2001) ("in holding an invention obvious in view of a combination of references, there must be some suggestion, motivation, or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in a way that would produce the claimed invention."); *and* (3) the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, hindsight analysis is not allowed. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) ("While the idea of using a monkey gene to probe for a homologous human gene may have been obvious to try, many pitfalls existed that would have eliminated a reasonable expectation of successfully obtaining the EPO gene. Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious."). Applicants respectfully submit that the Office has failed to make a *prima facie* case for obviousness.

While Vazquez et al. teaches compounds for inhibition of retroviral protease, it does not teach or suggest a method for treating human immunodeficiency virus (HIV) infection in an *antiretroviral treatment-experienced* mammal. Antiretroviral treatment-experienced

patients develop resistance, e.g., multidrug resistance. Inhibition of multi-drug resistant retroviral proteases, particularly multi-drug resistant HIV proteases is a major problem. As set forth in the background of the present application, the development of drug resistance is one of the most perplexing challenges in the field of medicine and one of the most dramatic and tragic examples of drug resistance can be found in connection with the antiviral therapy of acquired immune deficiency syndrome (AIDS). While there are many drugs on the market for treating AIDS, the available options for multi-drug resistant AIDS therapy and/or HIV management is severely limited or is otherwise completely nonexistent. Options available for antiretroviral treatment-experienced patients are minimal.

New mutant strains of HIV have emerged that are resistant to multiple, structurally diverse, experimental and chemotherapeutic inhibitors. Such multidrug-resistant retroviral protease strains are typically found in infected patients, who had undergone treatment with a combination of HIV protease inhibitors or series of different HIV protease inhibitors. Vazquez et al. does not address the daunting problem of treating antiretroviral treatment-experienced patients who are afflicted with multi-drug resistance. Based on the teachings in Vazquez et al., there is no suggestion that the compounds can be used against multi-drug resistant HIV proteases. Vazquez et al. does not suggest a method of treating human immunodeficiency virus (HIV) infection in an antiretroviral treatment-experienced mammal. Applicants have discovered a new property, a new method, which is neither disclosed nor suggested by the cited reference.

Those of ordinary skill in the art would know that an infected patient can be first treated with Vazquez et al.'s compounds. However, as soon as the first treatment is over, the virus is expected to develop a resistant strain. Such a patient, having a resistant strain of HIV, will likely not respond to the compounds of Vazquez et al. based on the teachings in the cited reference. Even if the compounds taught in the cited reference overlap with those of the presently claimed invention, there is no expectation, absent a glaring hindsight, that those compounds will work against a resistant strain in view of the mountain of evidence available in the art showing that treatment experienced individuals develop multi-drug resistant strains that are difficult to treat.

In addressing the claims which expressly require that the mammal be infected with a multidrug resistant mutant retrovirus or a multi-drug resistant HIV or a mutant virus having one reverse transcriptase mutation, the Office argues that Vazquez et al.'s statement that it has been shown that frameshift mutations in the protease region of the pol gene of HIV prevents processing of the gag precursor protein and that the gag protein is prevented through site-directed mutagenesis of an aspartic acid residue in the HIV protease active site. However, these teachings do not provide any indication that the compounds are active against treatment-experienced patients who have multidrug resistant proteases. The Office would fail to make a *prima facie* case for obviousness of the present claims. The Office did not comply with the mandate of the United States Supreme Court that the Patent Office must make it clear in the record that the teaching-suggestion-motivation to modify the reference exists. As emphasized by the Supreme Court, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex, Inc.*, No. 04-1350, slip op. at 14 (S. Ct. April 30, 2007). Further, there is so much unpredictability in the art of treating antiretroviral treatment-experienced individuals that the scant teaching if any in Vazquez et al. does not rise to the level of providing a reasonable expectation of success in arriving at the claimed invention.

Applicants have shown that compound 32 of the present invention, tested successfully against various multi-drug resistant HIV-1 strains clinically isolated from antiretroviral treatment-experienced patients (see Example 20). These isolates were all taken from patients who failed therapy on one or more HIV protease inhibitors due to high level of clinical resistance. Thus, compound 32 as tested against the multi-drug resistant clinical isolates side-by-side with known drugs that are commonly used in HIV antiviral therapy such as AZT, 3TC, DDI, DDC, and D4T, and protease inhibitors such as Indinavir, Nelfinavir, Ritonavir, and Saquinavir. The IC_{50} values for compound 32 and the comparative drugs are shown in Table 9a of the specification. The results show the effectiveness of a compound of the invention against a wide range of viral mutants compared to other well-known inhibitors of the HIV protease. Compound 32 was ten to one-thousand times more potent against these viruses than even Saquinavir, one of the most potent known compounds against multi-drug resistant HIV-1. Applicants have invented compounds which fulfill an unmet need in the treatment of multidrug resistant HIV.

As a further evidence of the inventive aspect of the claimed invention, compound 32 has received approval from the US FDA for co-administration with ritonavir for the treatment of HIV infection in *antiretroviral treatment-experienced* adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor; see attached copies of approval letter of June 2006 (NDA 21-976) and Full Prescribing Information on Prezista ™ (darunavir) tablets.

In view of all of the foregoing, the obviousness rejection should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

Xavier Pillai, Ph.D., Reg. No. 39,799
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson Avenue
Chicago, Illinois 60601-6731
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

Date: June 14, 2007

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-976

Tibotec, Inc.
Attention: Jenny Z. Lin, PharmD
Manager, Global Regulatory Affairs
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Dear Dr. Lin:

Please refer to your new drug application (NDA) dated December 22, 2005, received December 23, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PREZISTA (darunavir) tablets, 300 mg.

We acknowledge receipt of your submissions dated:

September 23, 2005	February 27, 2006	June 12, 2006
November 4, 2005	March 21, 2006	June 19, 2006
November 17, 2005	March 29, 2006	June 21, 2006
December 22, 2005	April 14, 2006	June 22, 2006
February 9, 2006	June 1, 2006	

This new drug application provides for the use of PREZISTA™ (darunavir) tablets, co-administered with 100 mg of ritonavir, for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

We completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed labeling text and patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the agreed upon enclosed labeling (text for the package insert and patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL, as soon as it is available but no more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material.

For administrative purposes, designate this submission "**FPL for approved NDA 21-976.**" Approval of this submission by FDA is not required before the labeling is used.

Submit content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your postmarketing study commitments specified in your submission dated June 22, 2006. These commitments, along with any completion dates agreed upon, are listed below.

1. By December 31, 2007, submit the final study reports and datasets of the 96-week data for the ongoing Phase 2b studies TMC114-C202, TMC114-C213, TMC 114-C208, and TMC114-C215.

2. By December 31, 2007, submit the final study reports and datasets of the 48 week data for the ongoing Phase 3 studies TMC114-C211 and TMC114-C214.

Please submit final study reports to NDA 21-976 as supplemental applications. For administrative purposes, all submissions relating to these postmarketing study commitments must be clearly designated "**Subpart H Postmarketing Study Commitments.**"

Furthermore, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 6 to 17 years until June 30, 2008. Also, we are deferring submission of your pediatric studies for less than 6 years of age until June 30, 2011.

Your deferred pediatric studies required under Section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

3. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients ages 6 to 17 years. Please assess the pharmacokinetics, safety, tolerability and antiviral activity of two alternative doses of a suitable pediatric formulation in combination with ritonavir, in treatment-experienced pediatric children and adolescents between 6 and 17 years of age.

Protocol Submission:	Completed
Final Report Submission:	24 week data by June 30, 2008

4. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients less than 6 years of age. Please evaluate dose requirements and safety in pediatric patients less than 6 years of age with HIV-1 infection after preliminary review of data from the 6 to 17 year olds in trial TMC114-C212 with the Division of Antiviral Products (DAVP).

Protocol Submission:	by December 31, 2008
Final Report Submission:	by June 30, 2011

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitments must be clearly designated **"Required Pediatric Study Commitments."**

In addition, we note the following postmarketing study commitments, specified in your submission dated June 22, 2006, that are not a condition of the accelerated approval. These commitments are listed below:

Drug-Drug Interaction Trials

5. Conduct an *in vivo* drug-drug interaction study between darunavir/rtv b.i.d. and rifabutin.

Protocol Submission:	by July 31, 2006
Final Report Submission:	by June 30, 2007

6. Conduct an *in vivo* drug-drug interaction study between darunavir/rtv b.i.d. and buprenorphine/naloxone.

Protocol Submission:	by December 31, 2006
Final Report Submission:	by January 31, 2008

7. Conduct an *in vivo* drug-drug interaction study between darunavir/rtv b.i.d. and carbamazepine.

Protocol Submission:	by December 31, 2006
Final Report Submission:	by January 31, 2008

Pharmacology/Toxicology

8. Complete the ongoing carcinogenicity study in mice and submit the final report.

Protocol Submission:	Completed
Final Report Submission:	by December 31, 2007

9. Complete the ongoing carcinogenicity study in rats and submit the final report.

Protocol Submission:	Completed
Final Report Submission:	by December 31, 2007

Pharmacokinetics

10. Please conduct a cocktail study to determine the effects of steady state darunavir/rtv 600/100 mg b.i.d. on the metabolism of CYP450 probe substrates for the following enzymes: CYP2C9, CYP2C19, and CYP2D6.

    Protocol Submission: by December 31, 2006
    Final Report Submission: by January 31, 2008

Special Populations

11. Evaluate the pharmacokinetics of darunavir/rtv in HIV-negative subjects with Child-Pugh A and Child-Pugh B liver disease in order to determine dosing recommendations.

    Protocol Submission: by July 31, 2006
    Final Report Submission: by March 31, 2007

12. Conduct a study of darunavir in treatment-experienced female patients to elucidate any potential gender differences in efficacy and safety.

    Protocol Submission: by December 31, 2006
    Final Report Submission: 24 week data by December 31, 2008

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

The following are not postmarketing study commitments; however, we request the following information be submitted:

Drug-Drug Interaction Trials

1. Please submit the results from your planned study TMC114-C127, a drug-drug interaction study between darunavir/rtv b.i.d. and methadone.

Clinical

2. In addition to the required periodic adverse drug experience reports [21 CFR 314.80(c)(2)], please submit a separate periodic adverse drug experience report for rash.

Microbiology

3. Determine response rates based upon presence of specific cleavage site mutations at baseline and submit this analysis with the PREZISTA traditional approval application.

4. Determine the protease cleavage site mutations that occur most frequently (>10%) in virologic failure isolates and submit this analysis with the PREZISTA traditional approval application.

5. Determine if the most frequently occurring protease cleavage site mutations contributed to decreases in darunavir susceptibility through site-directed mutagenesis and submit this analysis with the PREZISTA traditional approval application.

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Elizabeth Thompson, M.S., Regulatory Project Manager, at (301) 796-0824.

Sincerely,

{See appended electronic signature page}

Mark Goldberger, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

Attachment: approved draft labeling and patient package insert

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Cox
6/23/2006 04:12:29 PM
for Mark J. Goldberger, MD MPH

PREZISTA™* (Tibotec, Inc.) (darunavir) Tablets

Full Prescribing Information

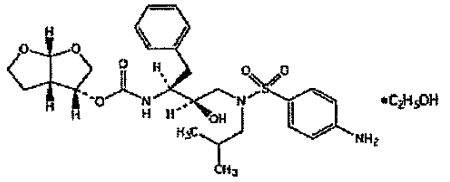
Manufactured for Tibotec, Inc. by:
JOLLC, Gurabo, Puerto Rico
Distributed by:
Tibotec Therapeutics,
Division of Ortho Biotech Products, L.P., Raritan, NJ 08869

PREZISTA™* (Tibotec, Inc.)
(darunavir)
Tablets

DESCRIPTION

PREZISTA™ (darunavir) is an inhibitor of the human immunodeficiency virus (HIV) protease.

PREZISTA™ (darunavir), in the form of darunavir ethanolate, has the following chemical name: [(1*S*,2*R*)-3-[[(4aminophenyl) sulfonyl](2-methylpropyl)amino]-2-hydroxy-1(phenylmethyl) propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*] furan-3-yl ester monoethanolate. Its molecular formula is $C_{27}H_{37}N_3O_7S \cdot C_2H_5OH$ and its molecular weight is 593.73. Darunavir ethanolate has the following structural formula:



Darunavir ethanolate is a white to off-white powder with a solubility of approximately 0.15 mg/mL in water at 20°C.

PREZISTA is available as an orange, oval-shaped, film-coated tablet for oral administration. Each tablet contains darunavir ethanolate equivalent to 300 mg of darunavir. Each tablet also contains the inactive ingredients colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. The tablet film coating, OPADRY® Orange, contains FD&C Yellow No. 6, polyethylene glycol 3350, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide.

All dosages for PREZISTA are expressed in terms of the free form of darunavir.

MICROBIOLOGY

Mechanism of Action
Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles.

Antiviral Activity
Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity in cell culture against a broad panel of HIV-1 group M (A, B, C, D, E, F, G), and group O primary isolates with EC_{50} values ranging from <0.1 to 4.3 nM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir did not show antagonism when studied in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir, the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine, the NNRTIs delavirdine, efavirenz, or nevirapine, and the fusion inhibitor enfuvirtide.

Resistance
Cell Culture: HIV-1 isolates with a decreased susceptibility to darunavir have been selected in cell culture and obtained from subjects treated with darunavir/ritonavir. Darunavir-resistant virus derived in cell culture from wild-type HIV had 6- to 21-fold decreased susceptibility to darunavir and harbored 3 to 6 of the following amino acid substitutions S37N/D, R41E/S/T, K55Q, K70E, A71T, T74S, V77I, or I85V in the protease. Selection in cell culture of darunavir resistant HIV-1 from nine HIV-1 strains harboring multiple protease inhibitor resistance-associated mutations resulted in the overall emergence of 22 mutations in the protease gene, including L10F, V11I, I13V, I15V, G16E, L23I, V32I, L33F, S37N, M46I, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82I, I84V, T91A/S, and Q92R, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight protease mutations and exhibited 50- to 641-fold decreases in darunavir susceptibility with final EC_{50} values ranging from 125 nM to 3461 nM.

Clinical studies of darunavir/ritonavir in treatment-experienced subjects
In the Phase 2b Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, multiple protease inhibitor-resistant HIV-1 isolates from highly treatment-experienced subjects who received PREZISTA/rtv 600/100 mg b.i.d. and experienced virologic failure, either by rebound, or by never being suppressed, developed amino acid substitutions that were associated with a decrease in susceptibility to darunavir. The amino acid substitution V32I developed on PREZISTA/rtv 600/100 mg b.i.d. in greater than 30% of virologic failure isolates and substitutions at amino acid position I54 developed in greater than 20% of virologic failure isolates. Other substitutions that developed in 10% to 20% of PREZISTA/rtv virologic failure isolates occurred at amino acid positions I15, L33, I47, G73 and L89. The median darunavir phenotype (fold change from reference) of the virologic failure isolates was 21-fold at baseline and 94-fold at failure. Amino acid substitutions were also observed in the protease cleavage sites of some darunavir virologic failure isolates. The resistance profile in treatment-naïve subjects has not been characterized.

Cross-Resistance
Cross-resistance among protease inhibitors has been observed. Darunavir has a <10-fold decreased susceptibility in cell culture against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to these protease inhibitors remain susceptible to darunavir. In Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, 60% (88/147) of subjects on darunavir/rtv whose baseline isolates had decreased susceptibility to tipranavir (tipranavir fold change >3) demonstrated a decrease of ≥1 $\log_{10}$ in viral load at week 24, and 36% (53/147) achieved <50 copies/mL plasma HIV RNA levels.

Darunavir-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir or saquinavir in cell culture. However, six of nine darunavir-resistant viruses selected in cell culture from protease inhibitor-resistant viruses showed a fold change in

EC_{50} values <3 for tipranavir, indicative of limited cross-resistance between darunavir and tipranavir. Of the viruses isolated from subjects experiencing virologic failure on darunavir/ritonavir 600/100 mg b.i.d., greater than 50% were still susceptible to tipranavir while less than 5% were susceptible to other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir).

Cross-resistance between darunavir and the nucleoside/nucleotide reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors or the fusion inhibitor is unlikely because the viral targets are different.

Baseline Genotype/Phenotype and Virologic Outcome Analyses
Genotypic and/or phenotypic analysis of baseline virus may aid in determining darunavir susceptibility before initiation of PREZISTA/rtv 600/100 mg b.i.d. therapy. Analyses were conducted to evaluate the impact of specific baseline protease inhibitor resistance-associated mutations and the number of protease inhibitor resistance-associated mutations at baseline on virologic response. Both specific mutations and the number of baseline mutations, as well as susceptible drugs in the optimized background regimen and enfuvirtide use, affected PREZISTA/rtv response rates in Phase 2b Studies TMC114-C213 and TMC114-C202.

The presence at baseline of the mutations V32I, I47V, or I54L or M, was associated with a decreased virologic response to darunavir and decreased susceptibility to darunavir. In addition, a diminished virologic response was observed in subjects with ≥7 protease inhibitor resistance-associated mutations (any change at amino acid positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, or 90) at baseline (see Table 1). In a supportive analysis of Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, the presence at baseline of three or more of the mutations V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V or L89V was associated with a decreased virologic response to PREZISTA/rtv (the proportion of subjects achieving viral load < 50 plasma HIV RNA copies/mL at week 24 was 50%, 22% and 10% when the baseline genotype had 0-2, 3 and ≥4 of these mutations, respectively). Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change pending additional data.

Table 1: Response to PREZISTA/rtv 600/100 mg b.i.d. by Baseline Number of Protease Inhibitor Resistance-Associated Mutations: As-Treated Analysis of Studies TMC114-C213 and TMC114-C202

	Prezista/rtv 600/100 mg (n=125)				Comparative Arm (n=120)			
PI Mutations^	n	Proportion of subjects with ≥1 log_{10} decrease at Week 24	Proportion of subjects with <50 copies/mL at Week 24	Median $DAVG_{24}$	n	Proportion of subjects with ≥1 log_{10} decrease at Week 24	Proportion of subjects with <50 copies/mL at Week 24	Median $DAVG_{24}$
0 - 4	57	81%	46%	-2.16	52	23%	13%	-0.57
5 - 6	54	67%	52%	-2.13	51	24%	16%	-0.43
≥7	14	21%	14%	-0.87	17	6%	0%	-0.13

^ Any change at protease amino acid positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88 and 90

Baseline darunavir phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome. Response rates assessed by baseline darunavir phenotype are shown in Table 2. These baseline phenotype groups are based on the select subject populations in the Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, and are not meant to represent definitive clinical susceptibility breakpoints for PREZISTA/rtv. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to darunavir in protease inhibitor-experienced patients.

Table 2: Response to PREZISTA/rtv 600/100 mg b.i.d. by Baseline Darunavir Phenotype: As-Treated Analysis of Studies TMC114-C213, TMC114-C202, and TMC114-C215/C208

Baseline Darunavir Phenotype N=340 (fold change ranges)	Proportion of subjects with ≥1 log_{10} decrease at Week 24	Proportion of subjects with <50 copies/mL at Week 24	Clinical Response Range
All Ranges	70% 238/340	43% 147/340	Overall Response
0-2	88% 119/136	60% 82/136	Higher than Overall Response
>2-7	73% 62/85	47% 40/85	Similar to Overall Response
>7-30	52% 33/63	24% 15/63	Lower than Overall Response
>30	43% 24/56	18% 10/56	Lower than Overall Response

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults
The pharmacokinetics of darunavir, co-administered with low dose ritonavir (100 mg twice daily), have been evaluated in healthy adult volunteers and in HIV-1 infected subjects. Table 3 displays the population pharmacokinetic estimates of darunavir from an analysis of integrated data from Studies TMC114-C213 and TMC114-C202 of 119 subjects administered the darunavir/ritonavir 600/100 mg b.i.d. dose. Darunavir is primarily metabolized by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir. When a single dose of 600 mg darunavir was given orally in combination with 100 mg ritonavir b.i.d., there was an approximate 14-fold increase in the systemic exposure of darunavir. Therefore, PREZISTA should only be used in combination with 100 mg of ritonavir to achieve sufficient exposures of darunavir.

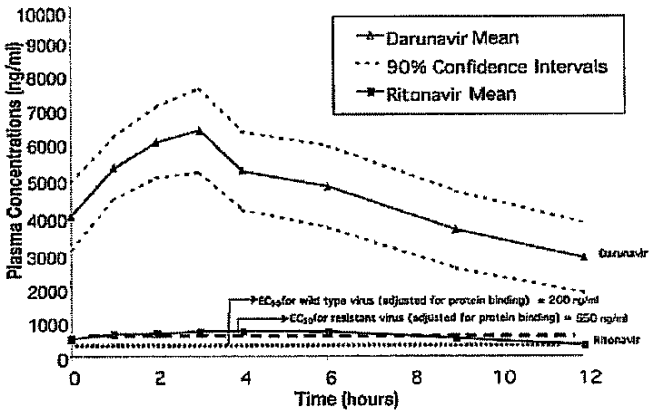
Table 3: Population Pharmacokinetic Estimates of Darunavir at the Darunavir/Ritonavir 600/100 mg b.i.d. dose (Integrated data from TMC114-C213 and TMC114-C202, Primary 24-Week Analysis)

Parameter	Darunavir/Ritonavir 600/100 mg b.i.d. N=119
AUC_{12h} (ng•h/mL)	
Geometric Mean ± Standard Deviation	62349 ± 16143
Median (Range)	61668 (33857-106490)
C_{0h} (ng/mL)	
Geometric Mean ± Standard Deviation	3578 ± 1151
Median (Range)	3539 (1255-7368)

N = number of subjects with data.

Figure 1 displays the mean plasma concentrations of darunavir and ritonavir at steady-state for the darunavir/ritonavir 600/100 mg b.i.d. dose.

Figure 1: Mean Steady-State Plasma Concentration-Time Profiles of Darunavir and Ritonavir at 600/100 mg b.i.d. at Week 4 (Integrated data from TMC114-C213 and TMC114-C202, Primary 24-Week Analysis)



Absorption and Bioavailability: Darunavir, co-administered with 100 mg ritonavir twice daily, was absorbed following oral administration with a T_{max} of approximately 2.5-4 hours. The absolute oral bioavailability of a single 600 mg dose of darunavir alone and after co-administration with 100 mg ritonavir twice daily was 37% and 82%, respectively.

Effects of Food on Oral Absorption: When administered with food, the C_{max} and AUC of darunavir, co-administered with ritonavir, is approximately 30% higher relative to the fasting state. Therefore, PREZISTA tablets, co-administered with ritonavir, should always be taken with food. Within the range of meals studied, darunavir exposure is similar. The total caloric content of the various meals evaluated ranged from 240 Kcal (12 gms fat) to 928 Kcal (56 gms fat).

Distribution: Darunavir is approximately 95% bound to plasma proteins. Darunavir binds primarily to plasma alpha 1-acid glycoprotein (AAG).

Metabolism: In vitro experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by CYP enzymes, primarily by CYP3A. A mass balance study in healthy volunteers showed that after a single dose administration of 400 mg ^{14}C-darunavir, co-administered with 100 mg ritonavir, the majority of the radioactivity in the plasma was due to darunavir. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 90% less than the activity of darunavir against wild-type HIV.

Elimination: A mass balance study in healthy volunteers showed that after single dose administration of 400 mg ^{14}C-darunavir, co-administered with 100 mg ritonavir, approximately 79.5% and 13.9% of the administered dose

of ^{14}C-darunavir was recovered in the feces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir. After intravenous administration, the clearance of darunavir, administered alone and co-administered with 100 mg twice daily ritonavir, was 32.8 L/h and 5.9 L/h, respectively.

Special Populations

Hepatic Impairment: Darunavir primarily undergoes hepatic metabolism. PREZISTA has not been studied in patients with varying degrees of hepatic impairment (see PRECAUTIONS, *Patients with co-existing conditions, Hepatic Impairment* and DOSAGE AND ADMINISTRATION).

Hepatitis B or Hepatitis C Virus Co-infection: The primary 24-week analysis of the data from Study TMC114-C213 in 31 HIV-1 infected subjects indicated that hepatitis B and/or hepatitis C virus co-infection status had no apparent effect on the exposure of darunavir.

Renal Impairment: Results from a mass balance study with ^{14}C-darunavir/ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine as unchanged drug. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n=20). There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease. (see PRECAUTIONS, *Patients with co-existing conditions, Renal Impairment,* and DOSAGE AND ADMINISTRATION).

Gender: Population pharmacokinetic analysis showed higher mean darunavir exposure (16.8%) in HIV infected females (n=68) compared to males. This difference is not clinically relevant.

Race: Population pharmacokinetic analysis of darunavir in HIV infected subjects indicated that race had no apparent effect on the exposure to darunavir.

Geriatric Patients: Population pharmacokinetic analysis in HIV infected subjects showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV infected subjects (n=12, age ≥65) (see PRECAUTIONS, *Geriatric Use*).

Pediatric Patients: The pharmacokinetics of darunavir in combination with ritonavir in pediatric patients has not been established. There are insufficient data at this time to recommend a dose.

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, *Drug Interactions*.

Darunavir and ritonavir are both inhibitors of CYP3A. Co-administration of darunavir and ritonavir with drugs primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase

or prolong their therapeutic effect and adverse events (see sections CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, *Drug Interactions*).

Darunavir and ritonavir are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir. Co-administration of darunavir and ritonavir and other drugs that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir.

Drug interaction studies were performed with darunavir and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of darunavir on the AUC, C_{max}, and C_{min} values are summarized in Table 4 (effect of other drugs on darunavir) and Table 5 (effect of darunavir on other drugs). For information regarding clinical recommendations, see PRECAUTIONS, *Drug Interactions*.

Table 4: Drug Interactions: Pharmacokinetic Parameters for Darunavir in the Presence of Co-Administered Drugs

Co-Administered Drug	Dose/Schedule: Co-Administered Drug	Dose/Schedule: Darunavir/rtv	N	PK	LS Mean Ratio (90% CI) of Darunavir Pharmacokinetic Parameters With/Without Co-Administered Drug No Effect =1.00: C_{max}	AUC	C_{min}
Co-Administration With Other Protease Inhibitors							
Atazanavir	300 mg q.d.^	400/100 mg b.i.d.†	13	↔	1.02 (0.96-1.09)	1.03 (0.94-1.12)	1.01 (0.88-1.16)
Indinavir	800 mg b.i.d.	400/100 mg b.i.d.	9	↑	1.11 (0.98-1.26)	1.24 (1.09-1.42)	1.44 (1.13-1.82)
Lopinavir/Ritonavir	400/100 mg b.i.d.	300/100 mg b.i.d.	9	↓	0.61 (0.51-0.74)	0.47 (0.40-0.55)	0.35 (0.29-0.42)
Saquinavir hard gel capsule	1000 mg b.i.d.	400/100 mg b.i.d.	14	↓	0.83 (0.75-0.92)	0.74 (0.63-0.86)	0.58 (0.47-0.72)
Co-Administration With Other Antiretrovirals							
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↓	0.85 (0.72-1.00)	0.87 (0.75-1.01)	0.69 (0.54-0.87)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.40‡ (1.14-1.73)	1.24‡ (0.97-1.57)	1.02‡ (0.79-1.32)
Tenofovir Disoproxil Fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.16 (0.94-1.42)	1.21 (0.95-1.54)	1.24 (0.90-1.69)
Co-Administration With Other Drugs							
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↔	0.83 (0.72-0.96)	0.87 (0.75-1.01)	1.01 (0.81-1.26)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	14	↑	1.21 (1.04-1.40)	1.42 (1.23-1.65)	1.73 (1.39-2.14)
Omeprazole	20 mg q.d.	400/100 mg b.i.d.	16	↔	1.02 (0.95-1.09)	1.04 (0.96-1.13)	1.08 (0.93-1.25)
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↔	0.97 (0.92-1.02)	1.02 (0.95-1.10)	1.07 (0.96-1.19)
Ranitidine	150 mg b.i.d.	400/100 mg b.i.d.	16	↔	0.96 (0.89-1.05)	0.95 (0.90-1.01)	0.94 (0.90-0.99)
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↔	1.01 (0.89-1.14)	0.98 (0.84-1.14)	0.94 (0.76-1.16)

N = number of subjects with data; - = no information available.
^q.d. = daily
† b.i.d. = twice daily
‡ Ratio based on between-study comparison.

Table 5: Drug Interactions: Pharmacokinetic Parameters for Co-Administered Drugs in the Presence of Darunavir/Ritonavir

Co-Administered Drug	Dose/Schedule: Co-Administered Drug	Dose/Schedule: Darunavir/rtv	N	PK	LS Mean Ratio (90% CI) of Co-Administered Drug Pharmacokinetic Parameters With/Without Darunavir No Effect =1.00: C_{max}	AUC	C_{min}
Co-Administration With Other Protease Inhibitors							
Atazanavir	300 mg q.d.^/ 100 mg RTV q.d. when administered alone 300 mg q.d. when administered with darunavir/ritonavir	400/100 mg b.i.d.†	13	↔	0.89 (0.78-1.01)	1.08 (0.94-1.24)	1.52 (0.99-2.34)
Indinavir	800 mg b.i.d./ 100 mg RTV b.i.d. when administered alone 800 mg b.i.d. when administered with darunavir/ritonavir	400/100 mg b.i.d.	9	↑	1.08 (0.95-1.22)	1.23 (1.06-1.42)	2.25 (1.53-3.10)
Lopinavir/Ritonavir	400/100 mg b.i.d.	300/100 mg b.i.d.	9	↑	1.22 (1.12-1.32)	1.37 (1.27-1.49)	1.72 (1.46-2.03)
Saquinavir hard gel capsule	1000 mg b.i.d./ 100 mg RTV b.i.d. when administered alone 1000 mg b.i.d. when administered with darunavir/ritonavir	400/100 mg b.i.d.	12	↔	0.94 (0.78-1.13)	0.94 (0.76-1.17)	0.82 (0.52-1.30)
Co-Administration With Other Antiretrovirals							
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↑	1.15 (0.97-1.35)	1.21 (1.08-1.36)	1.17 (1.01-1.36)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.18 (1.02-1.37)	1.27 (1.12-1.44)	1.47 (1.20-1.82)
Tenofovir Disoproxil Fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.24 (1.08-1.42)	1.22 (1.10-1.35)	1.37 (1.19-1.57)
Co-Administration With Other Drugs							
Atorvastatin	40 mg q.d. when administered alone 10 mg q.d. when administered with darunavir/ritonavir	300/100 mg b.i.d.	15	↑	0.56 (0.48-0.67)	0.85 (0.76-0.97)	1.81 (1.37-2.40)
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↑	1.26 (1.03-1.54)	1.57 (1.35-1.84)	2.74 (2.30-3.26)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	15	↑	2.11 (1.81-2.44)	3.12 (2.65-3.66)	9.68 (6.44-14.55)
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↓	0.64 (0.59-0.71)	0.61 (0.56-0.66)	0.53 (0.55-0.73)
Pravastatin	40 mg single dose	600/100 mg b.i.d.	14	↑	1.63 (0.95-2.82)	1.81 (1.23-2.66)	-
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↓	0.56 (0.49-0.63)	0.51 (0.45-0.59)	0.51 (0.45-0.57)
Sildenafil	100 mg (single dose) administered alone 25 mg (single dose) when administered with darunavir/ritonavir	400/100 mg b.i.d.	16	↑	0.62 (0.55-0.70)	0.97 (0.86-1.09)	-

N = number of subjects with data; - = no information available.
^q.d. = daily
† b.i.d. = twice daily

INDICATIONS AND USAGE

PREZISTA, co-administered with 100 mg ritonavir (PREZISTA/rtv), and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

This indication is based on Week 24 analyses of plasma HIV RNA levels and CD4+ cell counts from 2 controlled trials of PREZISTA/rtv in combination with other antiretroviral drugs. Both studies were conducted in clinically advanced, treatment-experienced (NRTIs, NNRTIs, and PIs) adult patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

The following points should be considered when initiating therapy with PREZISTA/rtv:

- Treatment history and, when available, genotypic or phenotypic testing, should guide the use of PREZISTA/rtv (see Microbiology).
- The use of other active agents with PREZISTA/rtv is associated with a greater likelihood of treatment response (see MICROBIOLOGY and INDICATIONS AND USAGE, Description of Clinical Studies).
- The risks and benefits of PREZISTA/rtv have not been established in treatment-naïve adult patients or pediatric patients.

Description of Clinical Studies
The evidence of efficacy of PREZISTA/rtv is based on the analyses of 24-week data from 2 ongoing, randomized, controlled trials, TMC114-C213 and TMC114-C202, in antiretroviral treatment-experienced HIV-1 infected adult subjects. These efficacy results were supported by the 24-week pooled analysis of the open label trials TMC114-C215 and TMC114-C208 of subjects who initiated PREZISTA/rtv at the recommended dose.

Treatment-Experienced Subjects:
Studies TMC114-C213 and TMC114-C202: These are ongoing randomized, controlled, Phase 2b trials consisting of 2 parts: an initial partially-blinded, dose-finding part and a second long-term part in which all subjects randomized to PREZISTA/rtv received the recommended dose of 600/100 mg b.i.d.

HIV-1 infected subjects who were eligible for these trials had plasma HIV-1 RNA > 1000 copies/mL, had prior treatment with PI(s), NNRTI(s) and NRTI(s), had at least one primary PI mutation (D30N, M46I/L, G48V, I50L/V, V82A/F/S/T, I84V, L90M) at screening, and were on a stable PI-containing regimen at screening for at least 8 weeks. Randomization was stratified by the number of PI mutations, screening viral load, and the use of enfuvirtide. Analyses included 318 subjects in Study TMC114-C213 and 319 subjects in Study TMC114-C202 who had completed 24 weeks of treatment or discontinued earlier.

At 24 weeks, the virologic response rate was evaluated in subjects receiving PREZISTA/rtv plus an optimized background regimen (OBR) versus a control group receiving an investigator-selected PI(s) regimen plus an OBR. Prior to randomization, PI(s) and OBR were selected by the investigator based on genotypic resistance testing

and prior ARV history. The OBR consisted of at least 2 NRTIs with or without enfuvirtide. Selected PI(s) in the control arm included: lopinavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%; 98% of control subjects received a ritonavir boosted PI regimen out of which 23% of control subjects used dual-boosted PIs. Approximately 47% of all subjects used enfuvirtide, and 35% of the use was in subjects who were ENF-naïve. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 $\log_{10}$ versus baseline.

In the pooled analysis for TMC114-C213 and TMC114-C202, demographics and baseline characteristics were balanced between the PREZISTA/rtv arm and the comparator PI arm. Table 6 compares the demographic characteristics between subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and subjects in the comparator PI arm.

Table 6: Demographic Characteristics of Subjects in the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/rtv 600/100 mg b.i.d. + OBR N=131	Comparator PI(s) + OBR N=124
Demographic Characteristics		
Age (years) (range, years)	43.0 (27-73)	44.0 (25-65)
Sex		
Male	89%	88%
Female	11%	12%
Race		
White	81%	73%
Black	10%	15%
Hispanic	7%	8%
Median Baseline Plasma HIV-1 RNA ($\log_{10}$ copies/mL) (range, $\log_{10}$ copies/mL)	4.52 (3.0-6.4)	4.56 (2.2-6.1)
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	153 (3-776)	163 (3-1274)
Percentage of Patients with Baseline Viral Load >100,000 copies/mL	24.4%	29.0%
Percentage of Patients with Baseline CD4+ Cell Count <200 cells/mm^3	67%	58%
Median Darunavir FC	4.3	3.3

Table 7 compares the baseline characteristics between subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and subjects in the comparator PI arm.

Table 7: Baseline Characteristics of Subjects in the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/rtv 600/100 mg b.i.d. + OBR N=131	Comparator PI(s) + OBR N=124
Baseline Characteristics		
Median Number of Resistance-Associated:		
PI mutations^	8	8
NNRTI mutations	1	1
NRTI mutations	6	5
Percentage of Subjects with the following Baseline IAS Primary Protease Mutations†:		
≤1	8%	13%
2	37%	25%
≥3	54%	62%
Median Number of ARVs Previously Used‡:		
NRTIs	6	6
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	5	5
Percentage of Subjects Resistant§ to All Available¶ PIs at Baseline, excluding Tipranavir	64%	61%
Percentage of Subjects with Prior Use of Enfuvirtide	19%	16%

^ L10F/I/R/V, K20I/L/M/R/T, L24I, D30N, V32I, L33F/I, M36I/L/V, M46I/L, I47A/V, G48V, I50L/V, F53L, I54A/L/M/S/T/V, A71V/T, G73A/C/S/T, V77I, V82A/F/L/S/T, I84A/C/V, N88D/S, L90M

† Based on the IAS-USA list of mutations (March 2005): D30N, L33F/I, M46I/L, G48V, I50L/V, V82A/F/L/S/T, I84A/C/V, L90M

‡ Only counting ARVs, excluding low-dose ritonavir, taken for at least 2 months, and for which start and stop dates were available

§ Based on phenotype (Antivirogram™)

¶ Commercially available PIs at the time of study enrollment

Week 24 outcomes for subjects on the recommended dose PREZISTA/rtv 600/100 mg b.i.d. from the pooled Studies TMC114-C213 and TMC114-C202 are shown in Table 8.

Table 8: Outcomes of Randomized Treatment Through Week 24 of the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/rtv 600 mg b.i.d. + OBR N=131	Comparator PI + OBR N=124
Virologic Responders confirmed at least 1 $\log_{10}$ HIV-1 RNA below baseline through Week 24 (<50 copies/mL at Week 24)	69.5% (45.0%)	21.0% (12.1%)
Virologic failures	26.0%	71.0%
Lack of initial response^	9.9%	57.3%
Rebound†	9.2%	9.7%
Never Suppressed‡	6.9%	4.0%
Death or discontinuation due to adverse events	3.9%	1.6%
Discontinuation due to other reasons	0.8%	6.5%

^ Subjects who did not achieve at least a confirmed 0.5 $\log_{10}$ HIV-1 RNA drop from baseline at Week 12

† Subjects with an initial response (confirmed 1 $\log_{10}$ drop in viral load), but without a confirmed 1 $\log_{10}$ drop in viral load at Week 24

‡ Subjects who never reached a confirmed 1 $\log_{10}$ drop in viral load before Week 24

Through 24 weeks of treatment, the proportion of subjects with HIV-1 RNA <400 copies/mL in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. compared to the comparator PI arm was 63% and 19%, respectively. In addition, the mean changes in plasma HIV-1 RNA from baseline were -1.89 $\log_{10}$ copies/mL in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. and -0.48 $\log_{10}$ copies/mL for the comparator PI arm. The mean increase from baseline in CD4+ cell counts was higher in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. (92 cells/mm^3) than in the comparator PI arm (17 cells/mm^3).

The TMC114-C215/C208 analysis: Additional data on the efficacy of PREZISTA/rtv 600/100 mg b.i.d. have been obtained in treatment-experienced subjects participating in the non-randomized trials TMC114-C215 and TMC114-C208. The 246 subjects from these trials included in the TMC114-C215/C208 24-week efficacy analysis initiated therapy with PREZISTA/rtv with the recommended dose of 600/100 mg b.i.d. The OBR consisted of at least two NRTIs with or without enfuvirtide. Entry criteria for the TMC114-C215/C208 analysis were the same as those for Studies TMC114-C213 and TMC114-C202.

Baseline characteristics of the subjects included in the TMC114-C215/C208 analysis were comparable to those subjects in Studies TMC114-C213 and TMC114-C202.

The TMC114-C215/C208 24-week efficacy analysis supported the viral load reduction and CD4+ cell count increases observed in the Studies TMC114-C213 and TMC114-C202. Of the 246 subjects at Week 24, 65% had a virologic response defined as a decrease of at least 1.0 $\log_{10}$ in plasma viral load versus baseline and 40% of the subjects reached less than 50 HIV-1 RNA copies/mL. The mean increase in CD4+ cell count versus baseline was 80 cells/mm^3 at Week 20. At Week 24, 57% of the subjects reached less than 400 HIV-1 RNA copies/mL, and the mean changes in plasma HIV-1 RNA from baseline were -1.65 $\log_{10}$ copies/mL.

CONTRAINDICATIONS

PREZISTA is contraindicated in patients with known hypersensitivity to any of the ingredients of the product.

Co-administration of PREZISTA/rtv is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These drugs are listed in Table 9 (also see PRECAUTIONS, Drug Interactions, Table 10).

Table 9: Drugs That Are Contraindicated With PREZISTA/rtv

Drug Class	Drugs Within Class That Are Contraindicated With PREZISTA/rtv
Antihistamines	Astemizole, Terfenadine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
GI Motility Agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Midazolam, Triazolam

Due to the need for co-administration of PREZISTA with 100 mg of ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications.

WARNINGS

ALERT: Find out about medicines that should not be taken with PREZISTA/rtv. This statement is included on the product's bottle label.

General
PREZISTA (darunavir) must be co-administered with ritonavir and food to exert its therapeutic effect (see DOSAGE and ADMINISTRATION). Failure to correctly administer PREZISTA with ritonavir and food will result in reduced plasma concentrations of darunavir that will be insufficient to achieve the desired antiviral effect.

Please refer to ritonavir prescribing information for additional information on precautionary measures.

Skin Rash
During the clinical development program, severe skin rash, including erythema multiforme and Stevens-Johnson Syndrome, has been reported. In some cases, fever and elevations of transaminases have also been reported. In clinical trials (n=924), rash (all grades, regardless of causality) occurred in 7% of subjects treated with PREZISTA; the discontinuation rate due to rash was 0.3%. Rashes were generally mild-to-moderate, self-limited maculopapular skin eruptions. Treatment with PREZISTA should be discontinued if severe rash develops.

Sulfa Allergy
Darunavir contains a sulfonamide moiety. PREZISTA (darunavir) should be used with caution in patients with a known sulfonamide allergy.

Drug Interactions
PREZISTA and ritonavir are both inhibitors of CYP3A. Co-administration of PREZISTA/rtv with drugs primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see sections CONTRAINDICATIONS and PRECAUTIONS, *Drug Interactions*).

Diabetes Mellitus / Hyperglycemia
New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between protease inhibitor therapy and these events have not been established.

PRECAUTIONS

Patients with co-existing conditions
Hepatic Impairment: Darunavir is primarily metabolized by the liver, hence, caution should be exercised when PREZISTA/rtv is given to patients with hepatic impairment, because increased plasma concentrations are expected in patients with hepatic impairment. There are no data regarding the use of PREZISTA/rtv when co-administered to patients with varying degrees of hepatic impairment; therefore, specific dosage recommendations cannot be made. PREZISTA/rtv should be used with caution in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults, Special Populations, Hepatic Impairment* and DOSAGE AND ADMINISTRATION).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, can have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening of liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal Impairment: Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n=20). There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease; however, since the renal clearance of darunavir is limited, a decrease in total body clearance is not expected in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults, Special Populations, Renal Impairment* and DOSAGE AND ADMINISTRATION).

Hemophilia: There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Fat Redistribution
Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome
During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium complex, cytomegalovirus,

Pneumocystis jeroveci pneumonia, and tuberculosis), which may necessitate further evaluation and treatment.

Resistance/Cross-Resistance
Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored in PREZISTA/rtv treated patients, it is unknown what effect therapy with PREZISTA will have on the activity of subsequently administered protease inhibitors.

Information for Patients
A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with PREZISTA.** A Patient Package Insert for PREZISTA is available for patient information.

Patients should be informed that PREZISTA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of PREZISTA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with PREZISTA can reduce the risk of transmitting HIV to others.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using PREZISTA.

Patients should be advised to take PREZISTA and ritonavir (NORVIR®) with food every day as prescribed. The type of food does not affect exposure to PREZISTA. Patients should be instructed to swallow whole tablets with a drink such as water or milk. PREZISTA must always be used with 100 mg of ritonavir (NORVIR®) in combination with other antiretroviral drugs. Patients should not alter the dose of either PREZISTA or ritonavir (NORVIR®), discontinue ritonavir (NORVIR®), or discontinue therapy with PREZISTA without consulting their physician. If a patient misses a dose of PREZISTA or ritonavir (NORVIR®) by more than 6 hours, the patient should be told to wait and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If the patient misses a dose of PREZISTA or ritonavir (NORVIR®) by less than 6 hours, the patient should be told to take PREZISTA and ritonavir (NORVIR®) immediately, and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If a dose of PREZISTA or ritonavir (NORVIR®) is skipped, the patient should not double the next dose. Inform the patient that he or she should not take more or less than the prescribed dose of PREZISTA or ritonavir (NORVIR®) at any one time.

PREZISTA/rtv may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort.

Patients receiving estrogen-based contraceptives should be instructed to use alternate contraceptive measures during therapy with PREZISTA/rtv because hormonal levels may decrease.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including PREZISTA/rtv, and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions
PREZISTA and ritonavir are both inhibitors of CYP3A. Co-administration of PREZISTA and ritonavir with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see Tables 10 and 11).

Drugs that are contraindicated and not recommended for co-administration with PREZISTA/rtv are included in Table 10. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 10: Drugs That Should Not Be Co-Administered With PREZISTA/rtv

Drug Class: Drug Name	Clinical Comment
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. PREZISTA/rtv should not be used in combination with phenobarbital, phenytoin, or carbamazepine as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	Rifampin is a potent inducer of CYP450 metabolism. PREZISTA/rtv should not be used in combination with rifampin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Gastrointestinal Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (*Hypericum perforatum*)	PREZISTA/rtv should not be used concomitantly with products containing St. John's wort (*Hypericum perforatum*) because co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis. For dosing recommendation regarding atorvastatin and pravastatin, see Table 11: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 11: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (See CLINICAL PHARMACOLOGY for Magnitude of Interaction, Tables 4 and 5)

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz	↓ darunavir ↑ efavirenz	Co-administration of darunavir/rtv and efavirenz decreased darunavir AUC by 13% and C_{min} by 31%. The AUC of efavirenz increased by 21% and C_{min} increased by 17%. The clinical significance has not been established. The combination of PREZISTA/rtv and efavirenz should be used with caution.
Nevirapine	↔ darunavir ↑ nevirapine	PREZISTA/rtv and nevirapine can be co-administered without any dose adjustments.
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Didanosine		It is recommended that didanosine be administered on an empty stomach. Therefore, didanosine should be administered one hour before or two hours after PREZISTA/rtv (which are administered with food).
Tenofovir Disoproxil Fumarate	↔ darunavir ↑ tenofovir	PREZISTA/rtv and tenofovir disoproxil fumarate can be co-administered without any dose adjustments.
HIV-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
Atazanavir (The reference regimen for atazanavir was atazanavir/ritonavir 300/100 mg q.d.)	↔ darunavir ↔ atazanavir	PREZISTA/rtv and atazanavir (300 mg q.d.) can be co-administered.
Indinavir (The reference regimen for indinavir was indinavir/ritonavir 800/100 mg b.i.d.)	↑ darunavir ↑ indinavir	The appropriate dose of indinavir in combination with PREZISTA/rtv has not been established.
Lopinavir/ritonavir	↓ darunavir ↑ lopinavir	Due to decrease in the exposure (AUC) of darunavir by 53%, appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer lopinavir/ritonavir and PREZISTA, with or without an additional low-dose of ritonavir.
Saquinavir	↓ darunavir ↔ saquinavir	Due to a decrease in the exposure (AUC) of darunavir by 26%, appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer saquinavir and PREZISTA, with or without low-dose ritonavir.
Other Agents		
Antiarrhythmics: bepridil, lidocaine (systemic), quinidine, amiodarone	↑ antiarrhythmics	Concentrations of bepridil, lidocaine, quinidine and amiodarone may be increased when co-administered with PREZISTA/rtv. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with PREZISTA/rtv.
Anticoagulant: warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations may be affected when co-administered with PREZISTA/rtv. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with PREZISTA/rtv.
Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and PREZISTA/rtv may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A inhibitor such as PREZISTA/rtv, the combination should be used with caution and a lower dose of trazodone should be considered.
Anti-infective: clarithromycin	↑ clarithromycin	No dose adjustment of darunavir or clarithromycin is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered: • For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50%. • For subjects with CLcr of <30 mL/min, the dose of clarithromycin should be reduced by 75%.
Antifungals: ketoconazole, itraconazole, voriconazole	↑ ketoconazole ↑ darunavir ↑ itraconazole (not studied) ↓ voriconazole (not studied)	Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole, and darunavir/ritonavir may increase plasma concentration of darunavir. Plasma concentrations of ketoconazole or itraconazole may be increased in the presence of darunavir/ritonavir. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Co-administration of voriconazole with darunavir/ritonavir has not been studied. Administration of voriconazole with ritonavir (100 mg twice daily) decreased the AUC of voriconazole by an average of 39%. Voriconazole should not be administered to patients receiving darunavir/ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Antimycobacterial: rifabutin	↑ rifabutin ↓ darunavir	Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and darunavir in the presence of ritonavir is expected to increase rifabutin plasma concentrations and decrease darunavir plasma concentrations. When indicated, it is recommended to administer rifabutin at a dosage of 150 mg once every other day when co-administered with PREZISTA/rtv.
Calcium Channel Blockers: felodipine, nifedipine, nicardipine	↑ calcium channel blockers	Plasma concentrations of calcium channel blockers (e.g. felodipine, nifedipine, nicardipine) may increase when PREZISTA/rtv are co-administered. Caution is warranted and clinical monitoring of patients is recommended.

Table 11: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (See CLINICAL PHARMACOLOGY for Magnitude of Interaction, Tables 4 and 5) (continued)

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir or Concomitant Drug	Clinical Comment
Corticosteroid: dexamethasone fluticasone propionate	↓ darunavir ↑ fluticasone propionate	Use with caution. Systemic dexamethasone induces CYP3A and can thereby decrease darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA. Concomitant use of inhaled fluticasone propionate and PREZISTA/rtv may increase plasma concentrations of fluticasone propionate. Alternatives should be considered, particularly for long term use.
HMG-CoA Reductase Inhibitors: atorvastatin pravastatin	↑ atorvastatin ↑ pravastatin	When atorvastatin and PREZISTA/rtv is co-administered, it is recommended to start with the lowest possible dose of atorvastatin with careful monitoring. A gradual dose increase of atorvastatin may be considered based on the clinical response. When PREZISTA/rtv was administered with pravastatin, the mean increase in pravastatin AUC was 81%. However, pravastatin AUC increased by up to 5-fold in some subjects. The mechanism of the interaction is not known.
H2-Receptor Antagonists and Proton Pump Inhibitors: omeprazole, ranitidine	↔ darunavir	PREZISTA/rtv can be co-administered with H2-receptor antagonists and proton pump inhibitors without any dose adjustments.
Immunosuppressants: cyclosporine, tacrolimus, sirolimus	↑ immunosuppressants	Plasma concentrations of cyclosporine, tacrolimus or sirolimus may be increased when co-administered with PREZISTA/rtv. Therapeutic concentration monitoring of the immunosuppressive agent is recommended for immunosuppressant agents when co-administered with PREZISTA/rtv.
Narcotic Analgesic: methadone	↓ methadone	When methadone is co-administered with PREZISTA/rtv, patients should be monitored for opiate abstinence syndrome, as ritonavir is known to induce the metabolism of methadone, leading to a decrease in its plasma concentrations. An increase in methadone dosage may be considered based on the clinical response.
Oral Contraceptives/ estrogen: ethinyl estradiol norethindrone	↓ ethinyl estradiol ↓ norethindrone	Plasma concentrations of ethinyl estradiol may be decreased due to induction of its metabolism by ritonavir. Alternative or additional contraceptive measures should be used when estrogen-based contraceptives are co-administered with PREZISTA/rtv.
PDE-5 Inhibitors: sildenafil, vardenafil, tadalafil	↑ PDE-5 inhibitors	Concomitant use of PDE-5 inhibitors with PREZISTA/rtv should be done with caution. If concomitant use of PREZISTA/rtv with sildenafil, vardenafil, or tadalafil is required, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours, is recommended.
Selective Serotonin Reuptake Inhibitors (SSRIs): sertraline, paroxetine	↔ darunavir ↓ sertraline ↓ paroxetine	If sertraline or paroxetine is co-administered with PREZISTA/rtv, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/rtv should be monitored for antidepressant response.

Other NRTIs:

Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir) that are primarily renally excreted, no drug interactions are expected for these drugs and PREZISTA/rtv.

Other protease inhibitors:

The co-administration of PREZISTA/rtv and PIs other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir has not been studied. Therefore, such co-administration is not recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis:

Long-term carcinogenicity studies of darunavir in rodents have not been completed. Darunavir, however, was tested negative in the *in vitro* Ames reverse mutation assay and *in vitro* chromosomal aberration assay in human lymphocytes, both tested in the absence and presence of metabolic activation system. Darunavir does not induce chromosomal damage in the *in vivo* micronucleus test in mice.

Impairment of Fertility:
There were no effects on fertility and early embryonic development with darunavir in rats and darunavir has shown no teratogenic potential in mice (in the presence or absence of ritonavir), rats and rabbits.

Pregnancy
Pregnancy Category B: Reproduction studies conducted with darunavir have shown no embryotoxicity or teratogenicity in mice, rats and rabbits. Because of limited bioavailability of darunavir in animals and/or dosing limitations, the plasma exposures (AUC values) were approximately 50% in mice and rats and 5% in the rabbit of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the rat pre- and postnatal development study, a reduction in pup body weight gain was observed with darunavir alone or in combination with ritonavir during lactation. This was due to exposure of pups to drug substances via the milk. Sexual development, fertility or mating performance of offspring was not affected by maternal treatment with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

There are, however, no adequate and well-controlled studies in pregnant women. PREZISTA should be used during pregnancy only if the potential benefit justifies the potential risk.

Antiretroviral Pregnancy Registry: *To monitor maternal-fetal outcomes of pregnant women exposed to PREZISTA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.*

Nursing Mothers
The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known whether darunavir is secreted in human milk, darunavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving PREZISTA.**

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Clinical studies of PREZISTA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of PREZISTA in elderly patients reflecting the greater frequency of decreased hepatic function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The safety assessment is based on all safety data from the Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis reported with the recommended dose PREZISTA/rtv 600/100 mg b.i.d. in the 458 subjects who initiated treatment with the recommended dose (*de novo* subjects). In Studies TMC114-C213 and TMC114-C202, the mean exposure in weeks for subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and comparator PI arm was 63.5 and 31.5, respectively. The mean exposure in weeks for subjects in the TMC114-C215/C208 analysis was 23.9.

The most common treatment-emergent adverse events (>10%) reported in the *de novo* subjects, regardless of causality or frequency, were diarrhea, nausea, headache, and nasopharyngitis.

For subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and the comparator PI arm in the pooled analysis for Studies TMC114-C213 and TMC114-C202, diarrhea was reported in 19.8% and 28.2%, nausea in 18.3% and 12.9%, headache in 15.3% and 20.2%, and nasopharyngitis in 13.7% and 10.5%, of subjects, respectively. In the randomized trials, rates of discontinuation of therapy due to adverse events were 9% in subjects receiving PREZISTA/rtv and in 5% of subjects in the comparator PI arm.

Due to the need for co-administration of PREZISTA with 100 mg of ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions.

Drug-related clinical adverse events of moderate or severe intensity (≥Grade 2) occurring in ≥ 2% of subjects treated with PREZISTA/rtv for 1 to 96 weeks are presented in Table 12.

Table 12: Percentage of Subjects with Selected Treatment Emergent, Drug-Related^ Adverse Events of at least Moderate Intensity (Grades 2-4) in ≥2% of Adult Subjects in Any PREZISTA/rtv Treatment Groups†

System Organ Class, Preferred Term, %	Randomized Studies TMC114-C213 and TMC114-C202		Non-randomized TMC114-C215/C208 Analysis
	PREZISTA/rtv 600/100 mg b.i.d. +OBR N=131	Comparator PI +OBR N=124	PREZISTA/rtv 600/100 mg b.i.d. +OBR N=327
Gastrointestinal Disorders			
Diarrhea	2.3%	3.2%	2.8%
Vomiting	1.5%	1.6%	2.4%
Abdominal Pain	2.3%	0.8%	1.2%
Constipation	2.3%	0.8%	0.6%
Nervous System Disorders			
Headache	3.8%	2.4%	0.9%

^ Includes adverse events at least possibly, probably, or very likely related to the drug
N=total number of subjects per treatment group
† Excludes laboratory abnormalities that were reported as Adverse Events (see Table 13: Treatment Emergent Grade 2 to 4 Laboratory Abnormalities Reported in ≥ 2% of Subjects)

Treatment-emergent adverse events occurring in less than 2% of *de novo* subjects (n=458) receiving PREZISTA/rtv, considered at least possibly related to treatment and of at least moderate intensity are listed below by body system:

Body as a Whole: folliculitis, asthenia, pyrexia, fatigue, rigors, hyperthermia, peripheral edema

Cardiovascular System: myocardial infarction, tachycardia, hypertension

Digestive System: flatulence, abdominal distension, dry mouth, dyspepsia, abdominal pain, nausea, constipation

Metabolic and Nutritional Disorders: anorexia, hypercholesterolemia, hyperlipidemia, diabetes mellitus, decreased appetite, obesity, fat redistribution, hyponatremia, polydipsia

Musculoskeletal System: arthralgia, pain in extremity, myalgia, osteopenia, osteoporosis

Nervous System: peripheral neuropathy, hypoesthesia, memory impairment, paresthesia, somnolence, transient ischemic attack, confusional state, disorientation, irritability, altered mood, nightmare, anxiety, headache

Respiratory System: dyspnea, cough, hiccups

Skin and Appendages: lipoatrophy, night sweats, allergic dermatitis, eczema, toxic skin eruption, alopecia, dermatitis medicamentosa, hyperhidrosis, skin inflammation, maculopapular rash, erythema multiforme, Stevens-Johnson Syndrome (reported in another ongoing clinical study)

Special Senses: vertigo

Urogenital System: acute renal failure, renal insufficiency, nephrolothiasis, polyuria, gynecomastia

Laboratory abnormalities: The percentages of adult subjects treated with PREZISTA/rtv 600/100 mg b.i.d. with treatment-emergent Grade 2 to 4 laboratory abnormalities are presented in Table 13.

Table 13: Treatment Emergent Grade 2 to 4 Laboratory Abnormalities Reported in ≥2% of Subjects

		Randomized Studies TMC114-C213 and TMC114-C202		Non-randomized TMC114-C215/C208 Analysis
Laboratory Parameter Preferred Term, %	Limit	PREZISTA/rtv 600/100 mg b.i.d. + OBR N=131	Comparator PI + OBR N=124	PREZISTA/rtv 600/100 mg b.i.d. N=327
Biochemistry				
Aspartate Aminotransferase	>2.5 X ULN	10.0%	13.0%	5.3%
Alanine Aminotransferase	>2.5 X ULN	6.9%	9.8%	5.6%
Gamma Glutamyl Transferase	>2.5 X ULN	9.2%	8.9%	8.4%
Hyperbilirubinemia	>1.5 X ULN	2.3%	15.4%	0.9%
Alkaline Phosphatase	>2.5 X ULN	4.6%	0%	2.8%
Pancreatic Amylase	>1.5 X ULN	16.9%	8.9%	10.8%
Pancreatic Lipase	>1.5 X ULN	8.5%	4.1%	6.2%
Hyperglycemia	≥161 mg/dL	2.3%	8.1%	5.9%
Hypoglycemia	≤54 mg/dL	1.5%	1.6%	3.7%
Total Cholesterol	≥240 mg/dL	9.2%	3.3%	8.0%
Triglycerides	>400 mg/dL	25.4%	26.0%	18.9%
Hypoalbuminemia	<3 g/dL	3.1%	1.6%	4.3%
Hyperuricemia	≥9.9 mg/dL	6.9%	6.5%	2.2%
Bicarbonate	<15 mmol/L	3.1%	4.1%	3.4%
Hypocalcemia	≤7.8 mg/dL	0%	0.8%	4.0%
Hyponatremia	≤129 meq/L	0.8%	0%	2.5%
Hypernatremia	≥151 meq/L	2.3%	0%	0%
Hematology				
White Blood Cell Count decrease	<3000 count/mm³	15.4%	18.7%	13.0%
Total Absolute Neutrophil Count decrease	≤999 mm³	6.9%	9.8%	11.5%
Lymphocytes decrease	<1000 count/mm³	4.6%	19.5%	10.9%
Partial Thromboplastin Time increase	>1.66 X ULN	7.8%	4.1%	4.3%
Plasma Prothrombin Time increase	>1.25 X ULN	3.9%	0.8%	0.6%
Platelet Count decrease	<75,000/mm³	3.1%	1.6%	2.8%

Patients co-infected with hepatitis B and/or hepatitis C virus:

Subjects co-infected with hepatitis B or C virus receiving PREZISTA/rtv, did not experience higher incidence of adverse events or clinical chemistry abnormalities than subjects receiving PREZISTA/rtv who were not co-infected. The pharmacokinetic exposure in co-infected subjects was comparable to that in subjects without co-infection. Standard clinical monitoring of patients with chronic hepatitis B and/or C is considered adequate.

OVERDOSAGE

Human experience of acute overdose with PREZISTA/rtv is limited. Single doses up to 3200 mg of the oral solution of darunavir alone and up to 1600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

There is no specific antidote for overdose with PREZISTA. Treatment of overdose with PREZISTA consists of general

supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since PREZISTA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

DOSAGE AND ADMINISTRATION

Adults: The recommended oral dose of PREZISTA tablets is 600 mg (two 300 mg tablets) twice daily taken with ritonavir 100 mg twice daily and with food. The type of food does not affect exposure to darunavir.

Pediatric Patients: The safety and efficacy of PREZISTA in pediatric patients has not been established (see CLINICAL PHARMACOLOGY, *Special Populations, Pediatric Patients*).

Hepatic Impairment: There are no data regarding the use of PREZISTA/rtv when co-administered to patients with varying degrees of hepatic impairment; therefore, specific dosage recommendations cannot be made. PREZISTA/rtv should be used with caution in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults, Special Populations, Hepatic Impairment* and PRECAUTIONS, Patients with co-existing conditions, Hepatic Impairment).

Renal Impairment: No dose adjustment is required in patients with moderate renal impairment. There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults, Special Populations, Renal Impairment* and PRECAUTIONS, *Patients with co-existing conditions, Renal Impairment*).

HOW SUPPLIED

PREZISTA (darunavir) tablets are supplied as orange, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 300 mg of darunavir per tablet. Each tablet is debossed with "300" on one side and "TMC114" on the other side. PREZISTA tablets are packaged in bottles in the following configuration:

300 mg tablets—bottles of 120 (NDC 59676-560-01)

Storage:

Store PREZISTA tablets at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F).

Rx Only

Tibotec Therapeutics
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Tibotec Therapeutics, Division of Ortho Biotech Products, L.P.,
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 Revised: October 2006 10101701

PREZISTA™* (darunavir) Tablets

Patient Information about

PREZISTA (pre-ZIS-ta)
for HIV (Human Immunodeficiency Virus) Infection
Generic name: darunavir (da-ROO-nuh-veer)

ALERT: Find out about medicines that should NOT be taken with PREZISTA. Please also read the section "Who should not take PREZISTA?".

Please read this information before you start taking PREZISTA. Also, read the leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss your treatment with PREZISTA the first time you take your medicine and at regular checkups. You should remain under a doctor's care when using PREZISTA and should not change or stop treatment without first talking with a doctor.

WHAT IS PREZISTA?

PREZISTA is an oral tablet used for the treatment of HIV (Human Immunodeficiency Virus) infection in adults. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). PREZISTA is a type of anti-HIV drug called a protease (PRO-tee-ase) inhibitor.

HOW DOES PREZISTA WORK?

PREZISTA blocks HIV protease, an enzyme which is needed for HIV to multiply. When used with other anti-HIV medicines, PREZISTA may reduce the amount of HIV in your blood (called "viral load") and increase your CD4 (T) cell count. HIV infection destroys CD4 (T) cells, which are important to the immune system. The immune system helps fight infection. Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system and, thus, reduce the risk of death or infections that can happen when your immune system is weak (opportunistic infections). PREZISTA is always taken with and at the same time as 100 mg of ritonavir (NORVIR®), in combination with other anti-HIV medicines. PREZISTA should also be taken with food.

DOES PREZISTA CURE HIV OR AIDS?

PREZISTA does **not** cure HIV infection or AIDS. At present, there is no cure for HIV infection. People taking PREZISTA may still develop infections or other conditions associated with HIV infection. Because of this, it is very important for you to remain under the care of a doctor. Although PREZISTA is not a cure for HIV or AIDS, PREZISTA can help reduce your risks of getting illnesses associated with HIV infection (AIDS and opportunistic infection) and eventually dying from these conditions.

DOES PREZISTA REDUCE THE RISK OF PASSING HIV TO OTHERS?

PREZISTA does **not** reduce the risk of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. Never re-use or share needles.

Ask your doctor if you have any questions on how to prevent passing HIV to other people.

WHAT SHOULD I TELL MY DOCTOR BEFORE I TAKE PREZISTA?

Tell your doctor about all of your medical conditions, including if you:

- are allergic to sulfa medicines.
- have diabetes. In general, anti-HIV medicines, such as PREZISTA, might increase sugar levels in the blood.
- have liver problems.
- have hemophilia. Anti-HIV medicines, such as PREZISTA, might increase the risk of bleeding.
- are pregnant or planning to become pregnant. The effects of PREZISTA on pregnant women or their unborn babies are not known. You and your doctor will need to decide if taking PREZISTA is right for you. If you take PREZISTA while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.
- are breastfeeding. Do not breastfeed if you are taking PREZISTA. You should not breastfeed if you have HIV because of the chance of passing HIV to your baby. Talk with your doctor about the best way to feed your baby.

WHO SHOULD NOT TAKE PREZISTA?**

Together with your doctor, you need to decide whether taking PREZISTA is right for you.

Do not take PREZISTA if you:

- are allergic to darunavir or any of the other ingredients in PREZISTA
- are allergic to ritonavir (NORVIR®)
- take any of the following types of medicines because you could experience serious side effects:

Type of Drug	Examples of Generic Names (Brand Names)
Antihistamines (to treat allergy symptoms)	astemizole (Hismanal®) terfenadine (Seldane®)
Ergot Derivatives (to treat migraine and headaches)	dihydroergotamine (D.H.E. 45®, Migranal®) ergonovine ergotamine (Wigraine®, Ergostat®, Cafergot®, Ergomar®) methylergonovine
Gastrointestinal Motility Agent (to treat some digestive conditions)	cisapride (Propulsid®)
Neuroleptic (to treat psychiatric conditions)	pimozide (Orap®)
Sedative/hypnotics (to treat trouble with sleeping and/or anxiety)	midazolam (Versed®) triazolam (Halcion®)

CAN PREZISTA BE TAKEN WITH OTHER MEDICATIONS?**

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements, including St. John's wort (*Hypericum perforatum*). PREZISTA and many other medicines can interact. Sometimes serious side effects will happen if PREZISTA is taken with certain other medicines (see "Who should not take PREZISTA?").

Tell your doctor if you are taking estrogen-based contraceptives. PREZISTA might reduce the effectiveness of estrogen-based contraceptives. You must take additional precautions for birth control such as a condom.

Tell your doctor if you take other anti-HIV medicines. PREZISTA can be combined with some other anti-HIV medicines while other combinations are not recommended.

Tell your doctor if you are taking any of the following medicines:

Type of Drug	Examples of Generic Names (Brand Names)
Antiarrhythmics (to treat abnormal heart rhythms)	bepridil (Vascor®) lidocaine (Lidoderm®) quinidine amiodarone (Cordarone®)
Anticoagulants (to prevent the clotting of red blood cells called platelets)	warfarin (Coumadin®)
Anticonvulsants (to treat epilepsy and prevent seizures)	carbamazepine (Tegretol®, Carbatrol®) phenobarbital phenytoin (Dilantin®, Phenytek®)
Antidepressants	trazodone (Desyrel®)
Anti-infectives (to treat bacterial infections)	clarithromycin (Biaxin®)
Antifungals (to treat fungal infections)	ketoconazole (Nizoral®) itraconazole (Sporanox®) voriconazole (Vfend®)
Antimycobacterials (to treat bacterial infections)	rifabutin (Mycobutin®) rifampin (Rifadin®, Rifater®, Rifamate®)
Calcium Channel Blockers (to treat heart disease)	felodipine (Plendil®) nifedipine (Adalat®) nicardipine (Cardene®)
Corticosteroids (to treat inflammation or asthma)	dexamethasone (Decadron®) fluticasone propionate Advair Diskus®,Cutivate®, Flonase®, Flovent Diskus®)
HMG-CoA Reductase Inhibitors (to lower cholesterol levels)	atorvastatin (Lipitor®) lovastatin (Mevacor®) pravastatin (Pravachol®) simvastatin (Zocor®)

Immunosuppressants (to prevent organ transplant rejection)	cyclosporine (Sandimmune®, Neoral®) tacrolimus (Prograf®) sirolimus (Rapamune®)
Narcotic Analgesics	methadone
PDE-5 Inhibitors (to treat erectile dysfunction)	sildenafil (Viagra®) vardenafil (Levitra®) tadalafil (Cialis®)
Selective Serotonin Reuptake Inhibitors (SSRIs) (to treat depression, anxiety, or panic disorder)	paroxetine (Paxil®) sertraline (Zoloft®)

Tell your doctor if you are taking any medicines that you obtained without a prescription.

This is **not** a complete list of medicines that you should tell your doctor that you are taking. Know and keep track of all the medicines you take and have a list of them with you. Show this list to all of your doctors and pharmacists any time you get a new medicine. Both your doctor and your pharmacist can tell you if you can take these other medicines with PREZISTA. Do not start any new medicines while you are taking PREZISTA without first talking with your doctor or pharmacist. You can ask your doctor or pharmacist for a list of medicines that can interact with PREZISTA.

HOW SHOULD I TAKE PREZISTA?

Take PREZISTA tablets every day exactly as prescribed by your doctor. You must take ritonavir (NORVIR®) at the same time as PREZISTA. The usual dose is 600 mg (two 300 mg tablets) of PREZISTA, together with 100 mg (one 100 mg capsule) of ritonavir (NORVIR®), twice daily *every day*. It may be easier to remember to take PREZISTA and ritonavir (NORVIR®) if you take them at the same time every day. If you have questions about when to take PREZISTA and ritonavir (NORVIR®), your doctor can help you decide which schedule works for you.

Take PREZISTA and ritonavir (NORVIR®) **with food.** The type of food is not important. Swallow the whole tablets with a drink such as water or milk. Do not chew the tablets.

Continue taking PREZISTA and ritonavir (NORVIR®) unless your doctor tells you to stop. Take the exact amount of PREZISTA and ritonavir (NORVIR®) that your doctor tells you to take, right from the very start. To help make sure you will benefit from PREZISTA and ritonavir (NORVIR®), you must not skip doses or interrupt therapy. If you don't take PREZISTA and ritonavir (NORVIR®) as prescribed, the beneficial effects of PREZISTA and ritonavir (NORVIR®) may be reduced or even lost.

If you miss a dose of PREZISTA or ritonavir (NORVIR®) by more than 6 hours, wait and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If you miss a dose of PREZISTA or ritonavir (NORVIR®) by less than 6 hours, take your missed dose of PREZISTA and ritonavir (NORVIR®) immediately. Then take your next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time.

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You should always take PREZISTA and ritonavir (NORVIR®) together with food. If a dose of PREZISTA or ritonavir (NORVIR®) is skipped, do not double the next dose. Do not take more or less than your prescribed dose of PREZISTA or ritonavir (NORVIR®) at any one time.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF PREZISTA?

Like all prescription drugs, PREZISTA can cause side effects. The following is **not** a complete list of side effects reported with PREZISTA when taken either alone or with other anti-HIV medicines. Do not rely on this leaflet alone for information about side effects. Your doctor can discuss with you a more complete list of side effects.

Mild to moderate rash has been reported in 7% of subjects receiving PREZISTA. In some patients, PREZISTA has been reported to cause a severe or life-threatening rash. Contact your healthcare provider if you develop a rash. Your healthcare provider will advise you whether your symptoms can be managed on therapy or whether PREZISTA should be stopped.

As with other protease inhibitors, PREZISTA may cause side effects, including:

- high blood sugar (hyperglycemia) and diabetes. This can happen in patients taking PREZISTA or other protease inhibitor medicines. Some patients have diabetes before starting treatment with PREZISTA which gets worse. Some patients get diabetes during treatment with PREZISTA. Some patients will need changes in their diabetes medicine. Some patients may need new diabetes medicine.
- increased bleeding in patients with hemophilia. This may happen in patients taking PREZISTA as it has been reported with other protease inhibitor medicines.
- changes in body fat. These changes can happen in patients taking anti-HIV medicines. The changes may include an increased amount of fat in the upper back and neck, breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- immune reconstitution syndrome. In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

The most common side effects include diarrhea, nausea, headache, and common cold.

Tell your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

HOW SHOULD I STORE PREZISTA TABLETS?

Store PREZISTA tablets at room temperature (77°F (25°C)). Short-term exposure to higher or lower temperatures [from 59°F (15°C) to 86°F (30°C)] is acceptable. Ask your doctor or pharmacist if you have any questions about storing your tablets.

This medication is prescribed for your particular condition. Do not use it for any other condition or give it to anybody else. Keep PREZISTA and all of your medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, contact your local poison control center or emergency room immediately.

This leaflet provides a summary of information about PREZISTA. If you have any questions or concerns about either PREZISTA or HIV, talk to your doctor.

For additional information, you may also call Tibotec Therapeutics at 1-800-325-7504.

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